Bisphosphonate use and subsequent prescription of acid suppressants

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Aim

To determine the extent of prescribing of acid suppression agents associated with initiation of bisphosphonate therapy.

Methods

This was a case control study, performed within the General Practice Network, Australia. The main outcome measure was re-attendance within six weeks from index bisphosphonate prescription for acid suppression agents.

Results

Of the bisphosphonate cases, 2.9% [95% confidence interval (CI) 1.8, 3.9] returned within 6 weeks for a prescription for proton pump inhibitor, histamine 2 receptor antagonist or antacid, compared with 0.9% of control patients (95% CI 0.5, 1.2). However, the bisphosphonate cases had significantly higher rates of previous use of nonsteroidal anti-inflammatory agents. After controlling for previous nonsteroidal anti-inflammatory drug use, the increased use of acid suppression agents was statistically significant, the odds ratio = 3.21 (95% CI 2.02, 5.11).

Conclusion

Bisphosphonate use appears to be associated with increased use of acid suppressant agents within 6 weeks of first supply.

Introduction

Adverse oesophageal events associated with the use of bisphosphonates are well documented. Reports of oesophagitis, oesophageal ulceration or oesophageal stricture associated with bisphosphonate use have been commonly reported via spontaneous adverse drug reaction reporting mechanisms [1, 2] and via prescription event monitoring studies [3]. Reviews of the clinical trial results suggest the incidence of upper adverse gas-

trointestinal events associated with bisphosphonate use are not significantly greater than placebo [4–6], suggesting this adverse event can be minimized. In an environment where there is potential for extensive use of bisphosphonates, with estimates that as many as 30% of postmenopausal women may require treatment and even greater potential for use if these medicines were used for primary prevention of osteoporosis, it becomes important, where possible, to minimize the occurrence

of this adverse drug event. Despite widespread knowledge of this adverse event, no studies appear to have been published assessing the incidence of subsequent prescribing of acid suppression therapy following initiation of bisphosphonate therapy.

The aim of this study was to determine whether bisphosphonate use in clinical practice was associated with subsequent use of histamine 2 receptor antagonists, proton pump inhibitors or antacids within 6 weeks.

Methods

To investigate the association between prescribing of bisphosphonates and histamine 2 receptor antagonists (H2RAs), proton pump inhibitors (PPIs) or antacids, a case-control study was undertaken using data from the General Practice Research Network (GPRN) [7]. The GPRN is an on-going random sample of Australian GP users of the electronic patient management system *Medical Director*. The GPRN aims to maintain an active random sample of 300 GPs. Longitudinal de-identified patient data dating back to 1 January 1999 can be extracted and provided to the research team on an ongoing basis from active participants. Data are captured from the electronic patient record for patient demographics; prescribing; reasons for prescribing; reasons for visit; patient history; pathology and radiology requests; and clinical measurements (e.g. blood pressure, height, weight).

Cases were new users of bisphosphonates with no recent H2RA or PPI use. New users were defined as persons for whom no prescription for bisphosphonates, H2RAs or PPIs was recorded in the database in the previous 12 months, or on the day of the bisphosphonate prescription. The index prescription for the bisphosphonates included any prescription for alendronate, etidronate, pamidronate and residronate.

Two controls were selected for each case. Controls were matched for gender, 5 years age group and the practice they attended. The controls were also required to have been prescribed at least one medication in the same yearly quarter as their bisphosphonate case matches, and to have had no bisphosphonate use recorded in the previous year or within 6 weeks of this medication. However, as the pool of control patients may have been prescribed a medication in different yearly quarters, control patients could potentially match to more than one bisphosphonate patient. The matching process allowed only one control patient to match to one bisphosphonate patient. If a control patient appeared in more than one yearly quarter and matched to a bisphosphonate patient in both, then the later quarter was favoured as this maximized the number of matches

made. Other than the matching variables the choice of controls was at random.

The primary endpoint chosen for the study was re-attendance within 6 weeks of the index bisphosphonate prescription for prescription of H2RAs, PPIs or antacids. These were defined as any prescription for ranitidine, cimetidine, famotidine, nazatidine, omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole and any antacid drugs (ATC code A02A) currently available on the Australian market.

A 6-week follow-up period was chosen because patient event monitoring has demonstrated that most adverse events (73%) occur within the first month of therapy [8, 9].

χ^2 tests were used to examine differences between groups. Odds ratio estimates were calculated for the endpoint under study, using a logistic regression model controlling for previous nonsteroidal anti-inflammatory drug (NSAID) use and incorporating the study design (cluster sample) in the calculation of the standard errors [10].

To determine whether there was any attendance bias the set dates for recalls, reminders or reviews of patients in order to manage a patient's treatment, which is a facility within the computer program, were analysed. Prescribing of index medicines for both cases and controls at these attendances was assessed.

In line with privacy legislation in Australia and Royal Australian College of General Practice guidelines, there was signed consent for the participating doctors. The patient data were de-identified at the practice prior to sending it to the compiled dataset. However, patients were able to opt out of having their de-identified data included in the process.

Results

Overall, 1753 new users of bisphosphonates who had their first prescription between January 2000 and July 2003 were identified, along with 3341 matched controls. Table 1 provides the demographics of the two groups. The groups were similar with respect to age and gender; however, the bisphosphonate cohort had significantly greater prior use of NSAIDs. Table 2 shows that most prescriptions for bisphosphonates were for alendronate followed by risidronate, and that the majority of use was to treat osteoporosis.

Overall, 2.9% [95% confidence interval (CI) 1.8, 3.9] of the bisphosphonate cohort returned within 6 weeks for a prescription for PPI, H2RA or antacid, compared with 0.9% of control patients (95% CI 0.5, 1.2) (see Table 3). The calculated odds ratio was 3.21 (95% CI 2.02, 5.11), while adjusting for previous NSAID use.

Table 1

Patient demographics

	Bisphosphonate cases 1753	Control group 3341	
Gender	86% women 14% men	83% women 17% men	
Age >75 years, %	45.4	41.6	
Age 50–74 years, %	51.6	54	
Previous PPI or H2RA use in last year	None	None	
Previous NSAID use (excluding Cox 2) in last year*, %	13.2	10.4	$P = 0.003$
Previous NSAID use (including COX 2) in last year*, %	30.3	20.7	$P < 0.001$

PPI, Proton pump inhibitor; H2RA, histamine 2 receptor antagonist; NSAID, nonsteroidal anti-inflammatory drug.

Table 2

Bisphosphonates used, dosages and indications amongst the bisphosphonate cases

Medication	Indication for which medicine is subsidized in Australia	Number of patients on medicine	Percentage of total	Median prescribed daily dose
Alendronate sodium 10 mg	Osteoporosis	395	22.5	10.0
Alendronate sodium 40 mg	Paget's disease	45	2.6	40.0
Alendronate sodium 70 mg	Osteoporosis	977	55.7	10.0
Disodium etidronate 200 mg	Paget's disease	6	0.3	200.0
Disodium etidronate + calcium carbonate 200 mg per 1.25 g	Osteoporosis	100	5.7	200.0
Disodium pamidronate 90 mg	Paget's disease	1	0.1	—
Disodium pamidronate 90 mg per 10 ml	Paget's disease	1	0.1	2.9
Risedronate sodium 30 mg	Paget's disease	8	0.5	30.0
Risedronate sodium 35 mg	Osteoporosis	45	2.6	5.0
Risedronate sodium 5 mg	Osteoporosis	175	10.0	5.0

The majority of prescribing in both groups was for PPIs. Where a prescription for a PPI, H2RA or antacid was written, on 78% of occasions in the study group the prescription included initial supply plus five repeat prescriptions, which represents maximum supply and enables continuous treatment for 6 months. This compared with 62% of prescriptions for PPI, H2RA or antacids in the control group enabling maximum supply.

Eleven patients (0.6%) from the bisphosphonate cohort and 10 (0.3%) from the matched controls had a recall notice in their records to return within 6 weeks of being prescribed the index medication. In both cohorts none of the patients for whom a review was set returned

within 6 weeks and was prescribed a PPI, H2RA or antacid. This suggests that there was no association between planned recalls and the prescription of PPI, H2RA or antacids, and hence no attendance bias.

Discussion

The results of this case-control study revealed increased utilization of acid suppressant therapy within 6 weeks of initial supply of a prescription for a bisphosphonate compared with a matched control. Most of the increased use of acid suppressant therapy involved use of PPIs, with no increased use of antacids observed. This 6-week time period is the period in which adverse events asso-

Table 3

Supply of proton pump inhibitor (PPI), histamine 2 receptor antagonist (H2RA) or antacid within 6 weeks of index bisphosphonate prescription

	Cases <i>n</i> = 1753	Control <i>n</i> = 3341
Co-prescription of PPI, H2RA at time of index bisphosphonate prescription	None	None
Returned within 6 weeks for PPI	38 (2.2%)	15 (0.4%)
Returned within 6 weeks for H2RA	11 (0.6%)	12 (0.4%)
Returned within 6 weeks for Antacid	1 (0.1%)	2 (0.1%)
Returned within 6 weeks for PPI, H2RA or antacid	50 (2.9%)	29 (0.9%)

ciated with the medication are most likely to first appear and so these results may indicate increased adverse upper gastrointestinal events associated with bisphosphonate use. The increased prior use of nonsteroidal anti-inflammatory agents amongst the bisphosphonate cohort may have contributed to some of the observed effect, with coadministration of NSAIDs having the potential to exacerbate gastrointestinal symptoms; however, after controlling for this use, an increased effect was still observed. Analyses of the subsequent rate of acid suppressant therapy for each of the specific drugs within the class were not undertaken, as the sample sizes at this level of analysis were insufficient and there were different usage patterns of the daily and weekly formulations across the drugs.

The results raise interesting questions regarding management of potential gastrointestinal events associated with bisphosphonate use and the implications for healthcare costs. While adverse oesophageal events associated with bisphosphonate use are well known, it is suggested from the randomized controlled studies that this can be minimized [4–6]. Further research is required to determine if the observed increase in utilization of acid suppressing medicines found in this study is related to lack of adherence to administration protocols and whether this is related to the adequacy of instructions, education and follow-up to consumers regarding appropriate administration. The rates of coadministration of NSAIDs and bisphosphonates found in this study suggest that this group should be a particular focus of attention, as the use of both products may increase the likelihood of adverse gastrointestinal events [11].

While it may be considered that increased utilization of acid suppressing agents overall is small, the potential

use of bisphosphonates in primary prevention as well as treatment of osteoporosis means that many millions of people may be treated with bisphosphonates. It is estimated that 30% of postmenopausal women have osteoporosis [4] and that in the USA alone 10–20 million postmenopausal women have osteoporosis [8]. Even a small increase in utilization of acid suppressing agents could have a significant impact on healthcare costs, particularly where acid suppression therapy is ongoing. In this study, where a prescription for a PPI, H2RA or antacid was prescribed, 78% of the time this was for the maximum quantity providing 6 months' supply, suggesting sustained use of therapy once initiated, and the majority of the prescribing was for PPIs, the most expensive therapeutic choice. Where prescribing of bisphosphonates is common, this could add to healthcare costs, not to mention patient discomfort. Consideration needs to be given to how to minimize this adverse event in practice.

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